1. SCIENTIFIC ABSTRACT

The treatment of most metastatic solid tumors remains problematic with little impact using surgery, chemotherapy, or radiation therapy. The application of immunotherapy to the treatment of cancer has gained popularity due to the isolation of an increasing number of putative tumor antigens and a better understanding of how to activate antigen-specific immune responses, with most attention focusing on T-cell immunity. Vaccines provide a useful method for stimulating immune responses and have been intensely studied as a method of cancer therapy. Basic research on T-cell biology has now revealed that activation of T-cells depends on delivery of two signals. The first signal is derived from processed antigens that are presented by tumor cells or professional antigen-presenting cells. The second signal is provided by a distinct set of cell surface proteins collectively referred to as co-stimulatory molecules. Several co-stimulatory molecules have now been described, including B7.1, B7.2, CD40L, CD30L, ICAM-1, LFA-3, 4-1BB, 0X40, ICOS, and others. Furthermore, antigen-specific T-cells may be tolerized in peripheral tissues by lack of co-stimulatory molecule expression on antigen-bearing cells, such as tumor cells. Thus, vaccines have been generated that express both an antigen and a co-stimulatory molecule, as described below. However, in situations where the tumor antigen is not known, such vaccines are ineffective. The direct delivery of co-stimulatory molecules into a tumor mass is one strategy that circumvents this problem and may also provide a powerful mechanism for breaking peripheral tolerance. The goal of this protocol is to compare the effectiveness and safety of two such vaccines in the treatment of metastatic solid malignancies. The vaccines are developed from a fowlpox virus engineered to express the B7.1 co-stimulatory molecule (rF-B7.1) and a fowlpox virus expressing three co-stimulatory molecules, B7.1, ICAM- 1, and LFA-3 (rF-TRICOM).